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Fibrotic Eye Muscles, Axenfeld Anomaly, Flat Face, and Mild Developmental Retardation: A New Example of the Chitty Syndrome

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We have studied a girl with fibrotic extrinsic eye muscles, Axenfeld anomaly, unusual facial appearance, mild hydrocephaly, and neurodevelopmental delay. Her condition is similar to the one described recently in members of a single family by Chitty et al. [1991, Am J Med Genet 40:417–420]. We suggest that she represents a second example of what may be called the Chitty syndrome.

KEY WORDS: fibrotic eye muscles, Axenfeld anomaly, Möbius sequence, deficient eye movement

INTRODUCTION

When observing serious limitation of eye movements in a newborn infant, the Möbius sequence becomes prominent among the diagnostic proposals if major cranial and intracranial abnormalities have been ruled out. However if, anterior eye chamber dysgenesis of the Axenfeld type and a peculiar facial appearance are found in addition to impairment of ocular movement in a child with developmental delay, a recently described [Chitty et al., 1991] rare syndrome with autosomal dominant inheritance may be proposed as diagnosis.

CLINICAL REPORT

The proposita V.D. was born by caesarean section after 36 weeks of gestation. Following two miscarriages she was the first child of non-consanguineous parents. The G_3P_1 mother had a normal daughter from a previous marriage. Because of recurrent hemorrhages from the 4th month caused by placenta praevia, bedrest was observed for the remaining months of pregnancy. Birth weight was 3,780 g, length was 46 cm, and the occipitofrontal circumference (OFC) was not recorded. The infant was placed in an incubator with supplementary oxygen for 5 days. She was breastfed without any problems.

At birth lack of lateral eye movement was interpreted as due to bilateral abducens paralysis. She was also found to have excessive frontal bossing, hypertelorism, flat midface, "crumpled," and apparently low-set ears and antimongoloid slant of the palpebral fissures. At 6 months the child was hypotonic with considerable headlag and showed little spontaneous motion. Axial hypotonia was particularly evident when the infant was held prone. However, mild hypertonia in all limbs was also demonstrated. Besides the obvious 6th nerve palsy, the function of the other cranial nerves appeared intact. Ophthalmologic evaluation documented cross-fixation, and preferential fixation by the left eye. Evoking optokinetic nystagmus (OKN) could not elicit lateral eye movements. There was rotatory nystagmus. The Axenfeld anomaly was confirmed by slitlamp examination. The eye fundi were normal. The patient is shown in Figure 1A,B.

At 6 months a MRI brain scan showed slight asymmetry of the falx, tentorium and of the cerebellum itself (Fig. 2A,B). There was manifest enlargement of the basal cisterns but a normal brain stem. Supratentorially the entire ventricular system showed moderate enlargement with hypoplasia of the corpus callosum. There were neither grey nor white matter signal alterations but instead unequivocal enlargement of the subarachnoidal spaces in the frontal, temporal, and parietal regions.

At seven months the girl had a RSV pneumonia causing dehydration and requiring hospital admission. At that time a roentgenographic skeletal survey showed no physical abnormalities. At 9 months corrective eye surgery was unsuccessful because of the finding of complete "congenital fibrosis" of the internal rectus muscles. Hearing loss suspected by brainstem evoked auditory response at that time, was ruled out subsequently. The EEG was normal for age. The karyotype was 46,XX. Other examinations with normal results included routine urinalysis, biochemical and cytological study of blood and cerebrospinal fluid, echocardiographic evaluation, abdominal ultrasonography, and SSEP.

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Fig. 1. **A:** Patient at age 22 months. **B:** Patient at 32 months: normal function of facial muscles; eye movements remain very limited; anterior eye chamber dysgenesis not well visible.

At 15 months intra-oesophageal pH-measurement confirmed gastro-oesophageal reflux. The girl's muscle strength and general tonus had improved. She could sit and stand without support. Internal strabismus and impairment of eye movement persisted (Fig. 1). The deep tendon reflexes were normal. Social contact was considered adequate for age. At 17 months a repeat MRI-brain and orbitascan confirmed the impression of mild but generalized cerebrocortical hypoplasia (Fig. 2D). The lateral Mm. recti could not be visualized adequately (Fig. 2C). Hypoplasia or secondary atrophy of these structures can neither be proved nor ruled out.

At 32 months following corrective surgery which demonstrated also considerable atrophy of the lateral rectus muscles, the squint had ceased to be cosmetically significant (Fig. 1B). However, except downward gaze, eye movements remained very limited.

The mother, 25 years old at the patient's birth, had a broad face, mild dystopia canthorum, and some proptosis of the eyes, but neither a squint nor any anterior chamber anomaly on slitlamp examination. In pictures of her recently deceased father his widely spaced eyes and deep nasal root were readily apparent. Both individuals were mentally normal and apparently unaffected.

DISCUSSION

The proposita had a combination of widely spaced and mildly proptotic eyes, squint and limitation of lateral movement of eyes, mild antimongoloid slant of the palpebral fissures, low nose bridge, and flat mid-face. Axenfeld anterior eye chamber dysgenesis with prominent and centrally displaced Schwalbe ring with iris adhesions but without hypoplasia of the anterior iris stroma.

CT- and MRI-brain and orbita scans demonstrated communicating hydrocephalus with mild hypoplasia of grey and white matter. At the earlier eye surgery fibrosis of both medial eye muscles was observed. The atrophy of the lateral rectus muscles seen during surgery at 32 months, may explain in part their difficult visualisation in the MRI orbitascan obtained more than 1 year previously (Fig. 2C).

The initial hypotonia and delay in motor development was overcome during the second year of life. Although motor development remained slower than normal, serious mental handicap of a degree apparent at preschool age was not evident.

Some manifestations in this patient may fit into the Möbius sequence of central palsies of the 6th and 7th cranial nerves. However, frontal bossing, flat mid-face, apparently low set ears, and most importantly congenital anomalies of the anterior eye segment are not usually associated with the Möbius sequence. Moreover, in the proposita palsy of the facial nerves was not observed (Fig. 1B). Also, her downward gaze remained largely intact. MRI scans and/or autopsy in Möbius sequence patients shows no supratentorial cerebral abnormality, but focal brain-stem hypoplasia, calcification or necrosis instead, apparently due to focal hemodynamic dysfunction or anomalous vascular anatomy [Govaert et al., 1989; D'Cruz et al., 1993].

The Möbius sequence known to be of heterogeneous pathogenesis, has been diagnosed also in patients with complete absence of the horizontal rectus muscles and their replacement by fibrous tissue. In these instances as in the report by Traboulsi and Maumence [1986] the hypothesis of a primary mesodermal defect with secondary brainstem neuronal loss and that of a primary developmental defect or antenatal vascular disruption of brainstem motor nuclei could not be sorted out. In such patients however anterior chamber defects were not noticed.

In addition, the proposita had bilateral Axenfeld anomaly, prompting consideration of the Axenfeld-Rieger syndrome as an alternate diagnosis. The absence of specific Rieger type eye abnormalities in this patient makes the differentiation not less relevant because the Axenfeld and Rieger types of anomaly in the anterior chamber may be different only in degree and extent but not necessarily in pathogenesis. The entire spectrum of Axenfeld-Rieger eye abnormalities is thought to be due to anomalies and/or abnormal resorption of neural crest derived tissues [Shields, 1985; Traboulsi, 1993]. On the other hand, the diagnosis of the Rieger or the Axenfeld-Rieger syndrome is made in patients with anterior segment dysgenesis in addition to facial, dental, umbilical, skeletal, and cerebral abnormalities [De Hauwere et al., 1973; Fitch and Kaback, 1978; Cross et al., 1979].

However the proposita presented has eye muscle fibrosis and hypoplasia in addition to mild hypertelorism, proptosis bulbi, maxillar hypoplasia, downward slant of palpebral fissures, and Axenfeld anomaly. She lacks deafness and has a hypoplastic corpus callosum in contrast to the patients reported by De Hauwere et al. [1973], who had normal eye muscle function and absence of the corpus callosum.

The proposita differs from patients with the Möbius sequence. Her condition does not correspond to the clinically ill defined spectrum of the Axenfeld-Rieger syndrome, because of her intraorbital muscle fibrosis and/or hypoplasia.

Alternatively it may be concluded that V.D. represents a new example of a rare syndrome composed of partially absent eye muscles, hydrocephaly, skeletal

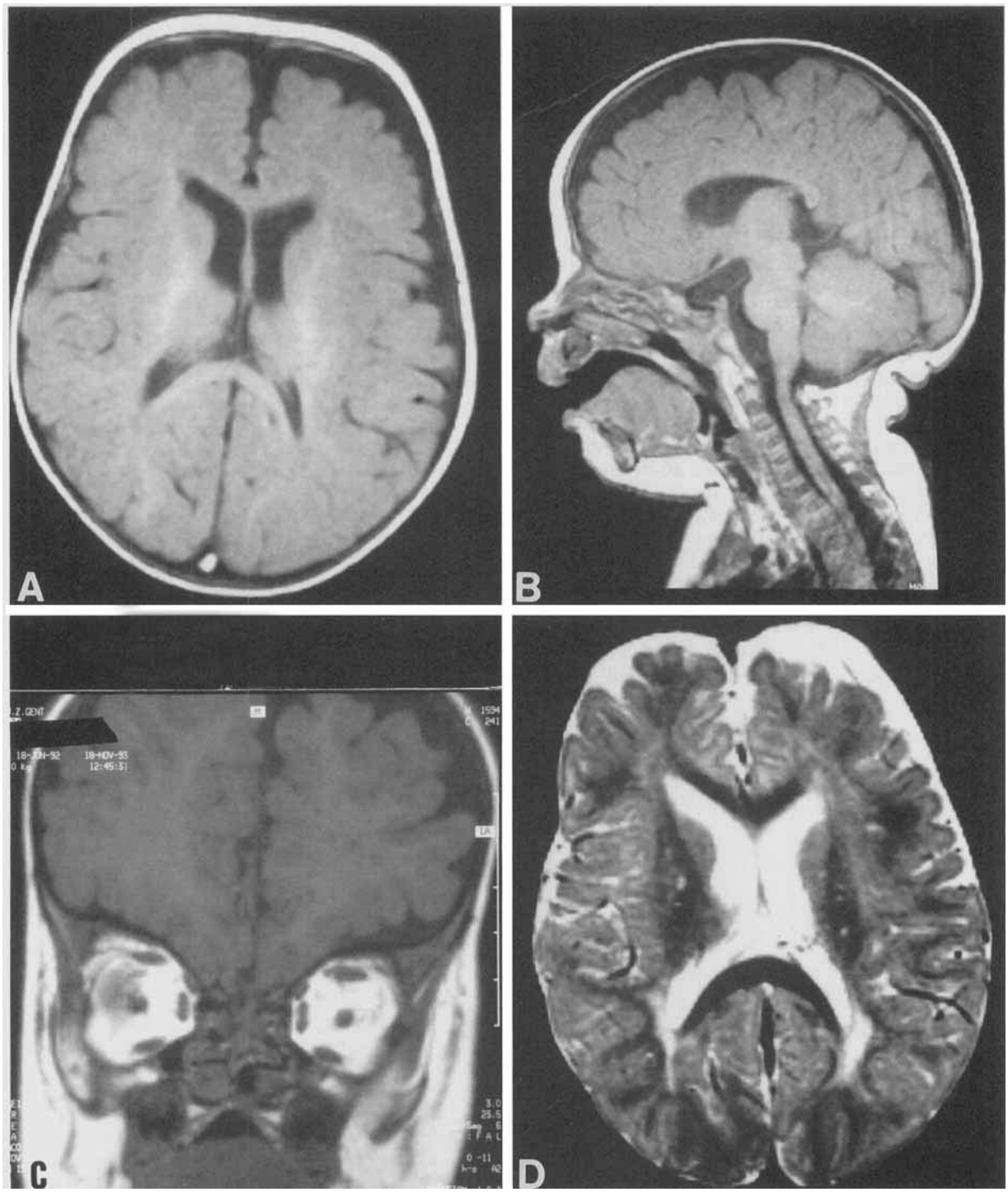

Fig. 2. MRI-scan (T_1 weighted) of brain at age six months. **A:** Enlarged frontal and temporoparietal subarachnoidal spaces; mild enlargement of frontal horns of lateral ventricles. **B:** Mild communicating hydrocephaly also apparent on lateral view. MRI scan at 17 months. **C:** Retro-orbital part of extrinsic eye muscles visible; lateral rectus muscles partly hidden within shadow of orbital wall. **D:** T_2-weighted image: stable enlargement of subarachnoidal and intraventricular spaces; some white matter alteration around occipital horns.

abnormalities and distinct facial appearance as recently described by Chitty et al. [1991]. The same syndrome was probably observed already by Sandall and Morrison [1979].

In our patient there is no sign of dysostosis or skeletal dysplasia. There is also no indication of craniosynostosis. However, her facial structure, anterior segment and eye muscle abnormalities appear to be strikingly similar to the craniofacial features in the reported patients. Although the authors provide no picture illustrating hydrocephalus in their patients [Chitty et al., 1991], it is described as being of the communicating but progressive type in one of them. There is no indication of such progression in the present patient, although her psychomotor development is mildly retarded. More definitive evaluation must await completion of a longer period of follow-up.

A cytogenetic abnormality detectable by classic banding methods has been ruled out. Contrary to the familial instances reported by Chitty et al. [1991], V.D. appears to be an isolated instance of the syndrome in her family unless mother's and maternal grandfather's facial appearance represents mild expression of the same condition.

The contention that this child is an additional example of Chitty syndrome may elicit some critical discussion on its delineation and the reporting of additional patients. From such facts and the accompanying debate the much needed clarification of the heterogeneous Axenfeld-Rieger syndrome would also benefit.

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